A Convenient Synthesis of 2-Amino-4-hydroxyquinolines

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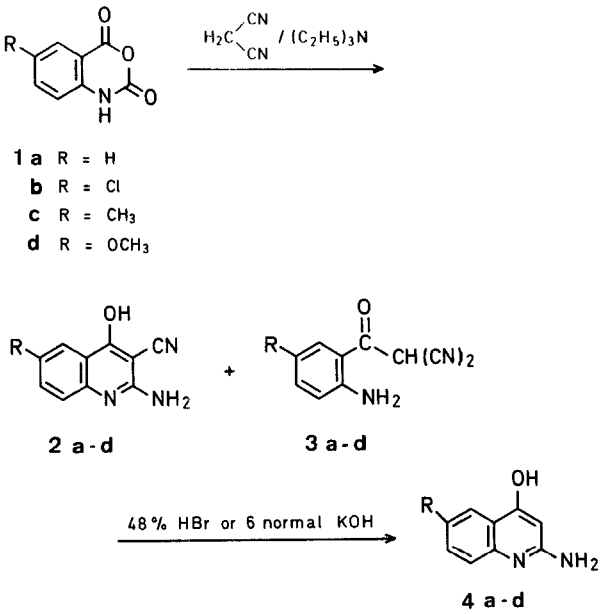
2-Amino-4-hydroxyquinolines are potentially versatile synthetic intermediates because they display reactive phenolic groups as well as nitrogen atoms that are suitably proximate for the construction of new heterocyclic rings. The synthetic procedure most suitable to the preparation of these quinoline derivatives has been that of Hardman and Partridge[1], in which anilinium benzenesulfonates or *p*-toluenesulfonates undergo fusion with ethyl cyanoacetate. However, this process not only affords low yields of products but also exhibits, as a consequence of the elevated reaction temperatures (>200°) required in the fusion process, inherent limitations as to the quantities of material that can be prepared in most laboratories during any single experiment.

We wish to report that when isatoic anhydride[2] (**1a**) or substituted isatoic anhydrides (**1b–d**) are treated with malononitrile under basic conditions and the resulting crude products (**2** and **3**) are subjected to hydrolytic/decarboxylative conditions, satisfactory yields of the appropriate 2-amino-4-hydroxyquinolines (**4a–d**) are obtained. The preparation of novel quinoline derivatives through analogous reactions of *N*-substituted isatoic anhydrides with various nucleophiles was recently reported[3].



Isatoic anhydrides (**1**), which either are available commercially or may be synthesized conveniently from suitable anthranilic acids and phosgene[4], react with brisk evolution of carbon dioxide when added to a warm solution of malononitrile and triethylamine in dimethylformamide. Aqueous, acidic work-up furnished isomeric mixtures (**2**+**3**) that exhibited expected mass spectral data, but which were not further purified since such attempts led to substances having altered physicochemical properties. Overnight hydrolysis of unpurified **2**+**3** (R = H, Cl, CH_3) in 48% hydrobromic acid provided the hydrobromide salts of the appropriate quinoline derivatives, aqueous solutions of which, upon basification, afforded **4** in 73–86% overall yields. As a consequence of the presence of a HBr-labile methoxy group, the preparation of 2-amino-4-hydroxy-6-methoxyquinoline (**4d**) utilized 6 normal potassium hydroxide as the hydrolysis medium.

2-Amino-4-hydroxyquinoline (4a):
A solution of isatoic anhydride (49.8 g, 0.3 mol) in dimethylformamide (300 ml) is added, during 30 minutes, to a warm (50–60°) solution of malononitrile (21.8 g, 0.33 mol) and triethylamine (33.4 g, 0.33 mol) in dimethylformamide (100 ml). Brisk evolution of carbon dioxide is observed, and the reaction mixture is maintained at 50–60° for 30 min after addition of the anhydride is complete. Upon pouring the resulting clear, dark solution into ice-cold 0.2 normal hydrochloric acid (2500 ml) a precipitate forms. This material is isolated by filtration and dried. It is then suspended in 48% hydrobromic acid (1500 ml) and the mixture refluxed for 20 h. The clear solution that results is chilled in an ice bath. A copious precipitate forms and is collected by filtration. This solid is dissolved in warm water and, after filtering to remove a small amount of insoluble material, the solution is made alkaline with ammonium hydroxide. Filtration, followed by washing with water and isopropanol, provides, after drying, **4a**; yield: 41.2 g (86%); m.p. 298–300° (dec.); Lit.[1] m.p. 301–302° (dec.). An analytical sample is recrystallized from methanol/water, m.p. 300° (dec.).

$C_9H_8N_2O$	calc.	C 67.47	H 5.03	N 17.49
(160.2)	found	67.23	5.12	17.50

M.S.: $m/e = 160$ ($M^{\oplus}$).

2-Amino-6-chloro-4-hydroxyquinoline (4b):
This material is prepared as described above except that the chloroisatoic anhydride (**1b**) is added as a suspension in dimethylformamide to a solution of malononitrile and triethylamine in dimethylformamide. Hydrolysis of intermediate (**2**+**3**) (R = Cl) with hydrobromic acid (35 ml acid/g) leads to the hydrobromide salt of **4b**. This is dissolved in hot 1:1 aqueous ethanol, and the solution made alkaline by the addition of ammonium hydroxide. Recrystallization of the product from methanol/water provides tan crystals; yield: 86%; m.p. 356° (dec.); Lit.[1] m.p. 358–361° (dec.).

$C_9H_7ClN_2O$	calc.	C 55.54	H 3.63	N 14.40
(194.6)	found	55.17	3.68	14.26

2-Amino-4-hydroxy-6-methylquinoline (4c):
This material is prepared from the appropriate methylisatoic anhydride[4,5] (**1c**), as described above for compound **4a**, except that in the hydrolysis of intermediate (**2**+**3**) ($R = CH_3$) a mixture of 48% hydrobromic acid (25 ml) plus acetic acid (5 ml) is utilized per gram of intermediate. The hydrobromide salt of **4c** is dissolved in warm 1:1 aqueous ethanol and the solution made alkaline by the addition of ammonium hydroxide; yield, 73%; m.p. 343° (dec.); Lit.[1] m.p. 341–342° (dec.).

$C_{10}H_{10}N_2O$	calc.	C 68.94	H 5.79	N 16.08
(174.2)	found	68.75	5.84	16.06

2-Amino-4-hydroxy-6-methoxyquinoline (4d):
This material is prepared from the appropriate methoxyisatoic anhydride[4,6], as described above for compound **4a**, except that

6 normal potassium hydroxide (20 ml/g) is used for the hydrolysis of **2**+**3** (R = OCH_3). The alkaline reaction mixture is acidified with acetic acid, and the resulting precipitate filtered free and then dissolved in aqueous ethanol. Addition of ammonium hydroxide affords **4d**; yield 69%; m.p. 298–300° (dec.); Lit.[1] m.p. 293–295° (dec.).

$C_{10}H_{10}N_2O_2$	calc.	C 63.14	H 5.30	N 14.73
(190.2)	found	62.85	5.23	14.56

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[1] R. Hardman, M. W. Partridge, *J. Chem. Soc.* **1954**, 3878.

[2] Isatoic anhydride is the trivial, but widely used and recognized name for 2*H*-3,1-benzoxazine-2,4(1*H*)-dione.

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[5] F. P. Woerner, H. Reimlinger, R. Merenyi, *Chem. Ber.* **104** 2786 (1971).

[6] T. Jen, B. Dienel, H. Bowman, J. Petta, A. Helt, B. Loev *J. Med. Chem.* **15**, 727 (1972).